Editorial Commentary

Is dismissing preoperative pregabalin premature?—the role of gabapentinoids in multimodal pain management following ureteroscopic stone surgery

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Ureteroscopic stone surgery has undergone wide scrutiny for post-operative pain management due to the high overall prevalence of the procedure, the wide variation in opioid and nonopioid prescribing patterns following routine ureteroscopy, and its accessibility as a target for quality improvement. Multiple cohort studies have suggested that a nonopioid approach to post-ureteroscopy symptom management is not only feasible but acceptable as the default prescribing regimen, although in practice there can be wide variation in adherence to these recommendations (1-3). Thus, optimizing nonopioid approaches to post-ureteroscopy recovery, including the use of adjunctive therapeutic classes, remains an active area of clinical investigation and relevance.

Gabapentinoids have typically been utilized for neuropathic pain and other neurologic symptoms, but some studies also report that gabapentinoids reduce pain after endourology procedures. Patients who received multiple weeks of pregabalin after ureteroscopy and laser lithotripsy with ureteral stent insertion had lower reported pain scores as compared to patients who only received solifenacin or placebo (4,5). A recent systematic review that included ten studies and 1,447 patients on the use of pregabalin and solifenacin concluded that pregabalin alone was effective for reducing ureteral stent-related pain, and that pregabalin and solifenacin combination therapy was best for reducing all stent-related symptoms (6). There remains a possibility that gabapentinoids can decrease post-ureteroscopy pain and play a role in nonopioid multimodal pain management.

A recently reported trial of preoperative pregabalin adds high-quality evidence to our understanding of pain management after ureteroscopy. Rosen *et al.* (7) randomized 118 patients undergoing ureteroscopy to receive a single dose of pregabalin 300 mg versus placebo one hour before surgery. The primary outcome was visual analogue scores (VAS) at one hour after surgery. Secondary outcomes included postoperative pain scores on post-op days 3, 7, and 30, emergency department visits, and opioid use. The authors found that patients who received pregabalin did not report lower postoperative pain. Indeed, the pregabalin group reported higher post-operative pain scores compared with the placebo group at post-op day 7. Although the pregabalin group was statistically younger, the higher pain scores persisted after controlling for age and preoperative pain. The authors concluded that single-dose of preoperative pregabalin offers no significant benefit to reduce post-ureteroscopy pain.

Interestingly, opioids were liberally prescribed to both groups in this study by contemporary standards. Two-thirds of patients overall were prescribed opioids at hospital discharge, with a median prescription of 50–60 mg oral morphine equivalents (OME), or about 7–8 oxycodone 5 mg tablets. By post-op day 30, the median total prescribed OME was 110 and 90 mg in the pregabalin and placebo groups, respectively, or about 12–15 oxycodone 5 mg tablets, a non-significant difference.

The considerable use of opioids for routine post-ureteroscopy symptom management in this trial warrants

attention. A 2020 multidisciplinary, multistakeholder panel consensus on opioid prescribing after endourological surgery recommended 0–10 oxycodone 5 mg tablets for opioid-naïve patients undergoing routine ureteroscopy and laser lithotripsy with ureteral stent placement, and 0–5 oxycodone 5 mg tablets for routine ureteroscopy and laser lithotripsy without stent placement (8). Notably, the minimum number of opioids recommended at discharge was zero for all procedures, indicating that clinicians should not feel obligated to prescribe opioids, nor should opioids be given if patients do not wish to use them.

Following a 2021 review of evidence, the panel updated its recommendations for ureteroscopy procedures and concluded that patients undergoing routine ureteroscopy and laser lithotripsy with ureteral stent placement should receive 0–5 oxycodone 5 mg tablets, while patients undergoing ureteroscopic procedures without stent placement or elective stent placement alone should not be prescribed opioids at all (9). These recommendations were guided by multiple studies demonstrating that most patients' symptoms could be managed with a multimodal nonopioid regimen, and that bothersome stent-related symptoms could be effectively controlled using nonopioid therapies. The panel also put forth comprehensive strategies to minimize unnecessary postoperative opioid prescribing, including setting appropriate patient expectations for pain control, maximizing routine use of nonopioid agents, and assessing patients' patterns of medication use before refilling opioid medications (9).

Our institutional practice for routine ureteroscopy procedures is a nonopioid discharge pathway that uses acetaminophen and nonsteroidal anti-inflammatory drugs (NSAID), plus alpha-blockers and/or anticholinergics as needed for specific stent-related symptoms unless contraindicated. We recognize that ureteroscopy is one of the most commonly performed procedures in urology, individual prescribing patterns may be influenced by local factors, and as cited in the Rosen study up to 15% of patients return to the emergency department within 30 days of surgery, primarily for pain control. However, we also take seriously that up to 40% of opioid overdoses in the United States are attributed to prescription medications, and that up to 6% of opioid-naïve patients become dependent once exposed to opioids after surgery (10,11). Thus, it is notable that the recommended amounts of prescribed opioids following ureteroscopy (0–5 oxycodone 5 mg tablets) are lower than the median quantities prescribed to patients the study by Rosen *et al.* and substantially lower than the 75th percentile of 30-day quantities prescribed (214 mg OME, or about 28 oxycodone 5 mg tablets, in the pregabalin group and 163 mg OME, or about 21 oxycodone 5 mg tablets, in the placebo group).

Although Rosen *et al.* reported a negative study, a continued emphasis on reducing opioid use for pain control after endoscopic surgery underscores the importance of investigating nonopioid medications such as gabapentinoids. In addition to acetaminophen, NSAIDs, alpha-blockers, and anticholinergics, multimodal regimens might include phenazopyridine, temporary intravesical lidocaine instillation, ice and heat packs, and gabapentinoids. We suggest that multiple forms of nonopioid pain management strategies should be employed when reasonably practical such that patients have several options to treat postoperative symptoms before resorting to opioids or seeking unplanned medical evaluation. Explaining the use and rationale of each management strategy can also provide mental reassurance to patients and reduce common anxiety about relying on "just in case" opioids. One explanation we share with patients is that a multimodal approach is akin to leaves slowing rainwater drainage from a rooftop gutter: one leaf may not significantly affect the outflow, but multiple leaves arranged in an overlapping and sequential manner can have a real—and in this case beneficial—effect on reducing symptoms.

In the context of the pregabalin study by Rosen *et al.*, is there any role for pregabalin in improving pain outcomes after ureteroscopy? Because pregabalin was given as a one-time 300 mg dose one hour before surgery, its postoperative impact might have been confounded by lingering anesthetic effects or its relatively rapid six-hour metabolic half-life as had been mentioned by other editorials accompanying the article. Perhaps alternative extended dosing regimens or prescribing pregabalin for longer duration post-operatively might provide more reliable and consistent effects. The authors did not report what other pain medications were routinely or consistently prescribed at discharge, nor how well pregabalin may have functioned when integrated with other nonopioid medications. Pre-procedural counseling and expectation-setting could also influence perceived pain after surgery, and we would welcome additional studies of patient-reported outcomes that integrate these strategies alongside medication.

While the pregabalin trial by Rosen *et al.* may have yielded a negative result, we do not believe that this study closes the door on gabapentinoids as a pain adjunct entirely. What this well-constructed study does suggest is that a single, preoperative dose of pregabalin may not

(yet) be optimized to yield demonstrable symptom relief—a commendable, incremental step toward a larger evidence base upon which to strengthen nonopioid pain mangement in urology.

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